. ATENT COOPERATION TRE TY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/005922	25.02.2005	25.02.2004

International Patent Classification (IPC) or both national classification and IPC
A61K45/06, A61K31/519, A61K39/395, A61K38/10, A61P35/00, A61K48/00

Applicant
DANA FARBER CANCER INSTITUTE, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/005922

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/005922

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-17 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 1-17 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/005922

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-17

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	13-15
	No:	Claims	1-12,16,17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	see the comments under Item III on separate sheet
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/005922

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1 to 17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no international preliminary examination will be made in respect of these claims with regard to industrial applicability (Article 34(4)(a)(i) PCT).

2. The present search revealed many documents relevant to the matter of lack of novelty and inventive step. A selection of the most relevant documents based on the features set out in the present dependent claims was made. A further search may, however, be necessary if and when the subject matter of the present claims is rendered *prima facie* novel.

Re Item IV
Lack of unity of invention

3. There is lack of unity of invention (Rule 13.1 PCT) in respect of the present claims. In this regard, there is no technical relationship involving one or more of the same or corresponding special technical features (Rule 13.2 PCT) between the subject-matter of the following groups of claims:

Invention subject (1); Claim 1 to 17; method of inhibiting tumour cell growth using a combination of a cytotoxic/ chemotherapeutic agent and insulin like growth factor receptor-1 (IGF-1R) inhibitor

Invention subject (2); Claim 18 to 32; method of inhibiting tumour cell growth using a combination of a compound which lowers the concentration of insulin-like growth factor and insulin- like growth factor receptor-1 (IGF-1R) inhibitor

Invention subject (3); Claims 33 to 38; method of inhibiting tumour cell growth using a combination of an anti-diabetic agent and insulin-like growth factor receptor-1 (IGF-1R) inhibitor

Invention subject (4); Claims 39 to 53 part; method of inhibiting tumour cell growth using a compound which decreases the expression of insulin- like growth factor receptor-1 (IGF-1R) inhibitor

Invention subject (5); Claims 39 to 59 part; method of inhibiting tumour cell growth or reducing angiogenesis or inducing apoptosis in a cell using an inhibitor of the activity of insulin- like growth factor receptor-1 (IGF-1R) wherein the inhibitor is a small molecule tyrosine kinase inhibitor

Invention subject (6); Claim 39 to 59 part; method of inhibiting tumour cell growth or reducing angiogenesis or inducing apoptosis in a cell using an inhibitor of the activity of insulin- like growth factor receptor-1 (IGF-1R) wherein the inhibitor is an anti-IGF1R neutralizing antibody

Invention subject (7); Claim 39 to 59 part; method of inhibiting tumour cell growth or reducing angiogenesis or inducing apoptosis in a cell using an inhibitor of the activity of insulin- like growth factor receptor-1 (IGF-1R) wherein the inhibitor is the IGF-1R antagonist JB-1

The detailed reasoning for this lack of unity is as set out in the Invitation to Pay Additional Fees (PCT/ISA/206)

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4. The documents cited in the International Search Report (ISR) are consecutively numbered D1 to D13 in the order of their listing. If not indicated otherwise, reference is made to the passages cited in said ISR.

5. Each of documents D1 to D12 discloses methods of inhibiting tumour cell growth using a combination of a cytotoxic/ chemotherapeutic agent and insulin like growth factor receptor-1 (IGF-1R) inhibitor. Thus, the subject matter of Claim 1 to 12,16 and 17 is not new in view of the disclosures of each of documents D1 to D12 (Article

33(2) PCT).

6. None of the presently available prior art documents appears to disclose the subject matter of any of Claims 13 to 15 (see however the warning herein above under Item III concerning the incomplete search). Thus, as far as can presently be determined, the subject matter of Claims 13 to 15 appears to be new (Article 33(2) PCT).

7. The subject matter of Claims 13 to 15 is however considered to lack inventive step for the following reasons; each of documents D1 to D12 disclose that combinations of cytotoxic/ chemotherapeutic agents and IGF-1R inhibitors have enhanced anti-tumour effects. The difference between the disclosure of each of these documents and the subject matter of Claims 13 to 15 is the selection of further IGF-1R inhibitors. It is considered that the selection of further IGF-1R inhibitors without any surprising technical effect is considered to be within the capability of the skilled man.

8. Thus, the subject matter of Claims 13 to 15 is not inventive in view of the disclosures of each of documents D1 to D12 (Article 33(3) PCT).

Re Item VI
Certain documents cited

9. The Applicant is warned that the disclosure of document D13 may become relevant in respect of novelty according national/regional patent law. This matter will be considered further by the relevant national/regional examining authorities, if and when the present application enters the national/regional phase(s).

Re Item VIII
Certain observations on the international application

10. The term "*cytotoxic or a chemotherapeutic agent*" in Claim 1 appears vague and unclear (Article 6 PCT). In this regard, it appears that almost any drug which may be administered with a view to eradicating cancer cells could be considered as a cytotoxic/ chemotherapeutic agent.

11. The definition of "*a preselected period of time*" in Claims 7 appears meaningless and redundant (Article 6 PCT).

12. The term "*sub-therapeutic*" in Claims 9 and 10 is vague and unclear. This claim fails to define how such sub-therapeutic doses could be used to treat tumour cell growth.

13. The definition of a "*small molecule tyrosine kinase inhibitor*" is vague and equivocal (Article 6 PCT)